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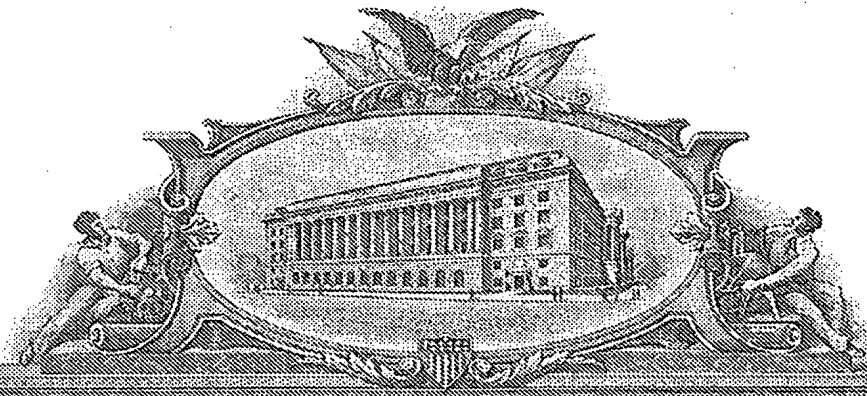
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**APPLICATION NUMBER: 10/815,414**

**FILING DATE: March 31, 2004**

**RELATED PCT APPLICATION NUMBER: PCT/US05/08839**



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for FY 2004**

Effective 10/01/2003. Patent fees are subject to annual revision.

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT (\$)

**Complete if Known**

Application Number	
Filing Date	March 31, 2004
First Named Inventor	Arnold Takemoto
Examiner Name	
Art Unit	
Attorney Docket No.	ATAKEM-001-USA

**METHOD OF PAYMENT (check all that apply)**☒ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None☒ Deposit Account:Deposit  
Account  
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Deposit  
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☒ Charge fee(s) indicated below ☒ Credit any overpayments☒ Charge any additional fee(s) or any underpayment of fee(s)☒ Charge fee(s) indicated below, except for the filing fee to the above-identified deposit account.**FEE CALCULATION****1. BASIC FILING FEE**

Large Entity		Small Entity		Fee Description	Fee Paid
Fee Code	Fee (\$)	Fee Code	Fee (\$)		
1001	770	2001	385	Utility filing fee	385
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

SUBTOTAL (1) (\$) 385

**2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE**

Total Claims	Extra Claims	Fee from below	Fee Paid
Independent	-20** =	X	
Multiple Dependent	-3** =	X	

Large Entity		Small Entity		Fee Description
Fee Code	Fee (\$)	Fee Code	Fee (\$)	
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) (\$)

\*\*or number previously paid, if greater; For Reissues, see above

**FEE CALCULATION (continued)****3. ADDITIONAL FEES**

Large Entity Small Entity

Fee Code	Fee (\$)	Fee Code	Fee (\$)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for <i>ex parte</i> reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	
1402	330	2402	165	Filing a brief in support of an appeal	
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,330	2453	665	Petition to revive - unintentional	
1501	1,330	2501	665	Utility issue fee (or, reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1808	180	1808	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR 1.129(e))	
1810	770	2810	385	For each additional invention to be examined (37 CFR 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify)

\*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) (\$)

**SUBMITTED BY**

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Date

March 31, 2004

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10/815414

033104

# **APPLICATION FOR UNITED STATES PATENT**

**in the name of**

**Arnold C. Takemoto**

**of**

**Immune Nutraceuticals, Inc.**

**for**

**Breast health preparations**

I hereby certify under 37 CFR 1.10 that this correspondence is being deposited with the United States Postal Service as Express Mail Post Office To Addressee with sufficient postage on the date indicated below and is addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231.

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**Gregory H. Shen**

name

**DATE OF DEPOSIT: 03/31/2004**

**EXPRESS MAIL NO.: ER 967546999 US**

# **Breast health preparations**

## **FIELD OF THE INVENTION**

This invention relates to preparations comprising beneficial phytochemical ingredients that are serviceable as health supplements for the body, particularly tissues susceptible to cancer, including, e.g. prostate tissue and breast tissue and, including, e.g., female breast tissue.

This invention also relates to preparations comprising chelating agents that are serviceable for the heavy metal detoxification of humans and animals and that can, in non-limiting fashion, be administrated orally, parenterally, or transdermally. In non-limiting exemplifications, this invention provides novel preparations of chelating agents encapsulated in micelles or liposomes comprising the triple combination of 1) micelles or liposomes comprising alpha lipoic acid and 2) micelles or liposomes comprising EDTA or other chelators; and furthermore, in different embodiments, 3) magnesium chloride is optionally an additional ingredient in these novel preparations.

This invention also relates to combinations, such as kits, comprising both a preparation of chelating agents, and a preparation of phytochemical ingredients.

## **RELATED APPLICATIONS**

Priority is claimed to provisional application Ser. No. (Not yet assigned), filed March 17, 2004, and entitled: Detoxification and chelating preparations that can be administrated orally, parenterally, and transdermally, and related methods. This application is a continuation-in-part of Ser. No. 10/804264, filed March 18, 2004, and entitled: Preparations of encapsulated bioavailable chelating agents for detoxifying humans and animals.

## **BACKGROUND OF THE INVENTION**

### **Tissue Health**

The ability to maintain the health of and to achieve the detoxification of tissues can be aided by many dietary supplements. However, in disease states, e.g. cancer, the cause of the disease may become refractory or resistant to a single-pronged approach to health and detoxification. Thus, this invention provides multi-pronged approaches that make advantageous use of novel combinations of ingredients that provide beneficial effects.

### **Toxicity and poisoning.**

Heavy metal poisoning is a serious medical problem that is receiving even more emphasis in recent years as the ability to detect toxic metals as well as the ability to understand the detrimental affects associated therewith have progressed compared to the past. Furthermore, it is known that toxic heavy metals such as lead and mercury may very easily enter the body as a consequence of, to name a few examples, accumulated exposure, accidents, environmental pollution, and oral consumption (e.g. food or paint). For example, exposures to lead and mercury are wide-spread and well documented. Poisoning from excessive concentrations of substances that would other wise be beneficial at lower concentrations is also known; e.g. iron poisoning has been reported. Arsenic can get into the body, e.g. as a result of industrial pollution. Also of concern are radioactive toxic heavy metals that pose an additional problem due to their radioactivity. These must be eliminated as quickly as

possible, because the ionizing radiations of the radioactive metals pose the risk of tumor induction from their radioactive ionization, including by altering DNA. Toxic heavy metals are also known to concentrate in various organs of the body. Plutonium, for example, usually deposits in the liver, and it is known that as much as 30 to 60% or more of an administered amount of plutonium will oftentimes deposit in the liver. The toxic heavy metal, plutonium in this example, remains in the organ and is only very slowly removed, thereby increasing the potential for tumors.

#### **Summary of challenges with traditional treatments.**

- 1) I.v. chelation is expensive, time-consuming, and has poor patient compliance.
- 2) Traditional oral chelation therapies are cheaper, but they are relatively ineffective at their intended purposes, and, at higher doses, are accompanied by side effects. For example, the oral administration of chelating agents by traditional approaches is problematic not only because their poor absorption and bioavailability prevents them from reaching the bodily stores of toxins and heavy metals, but furthermore they can chelate beneficial substances in the digestive tract.
- 3) Using traditional therapies, neither parenterally (e.g. by i.v.) nor orally administered chelating agents are able to enter the intracellular compartments where toxins and heavy metals are also present. Traditional therapies for the parenteral administration of chelating agents using physiologically compatible aqueous solutions (e.g. saline, Ringer's solution, etc.), fail to cause absorption of lipid soluble agents, because of inherent solubility problems.



### **1) Challenges with i.v. chelation therapies.**

Heavy metal detoxification can be accomplished using i.v. chelation with ingredients such as EDTA; this approach has been documented to be effective and safe, and EDTA was approved by the FDA for this use in the 1950's. The ability of i.v. chelation therapy to diminish and even dissolve arterial plaques has also been reported. However, i.v. chelation is very expensive and time-consuming, typically requiring a patient make a series of 20 to 50 visits to a physician's office or hospital (at least 30 visits are typically required), with each visit often taking from 3-4 hours, during which time the patient is typically seated, and costing up to \$100 or more per visit.

### **2) Challenges with orally administered chelation therapies.**

Oral chelation products are commercially available, and they are marketed as much less expensive alternatives to i.v. chelation therapies. However, EDTA is very poorly absorbed when administered by mouth; and the general consensus is that typically only about five percent is absorbed. Although even that small amount does remove lead from the body, it also been reported to increase the absorption of lead.

Other serious potential problems have been reported as well. For example, it has been reported that the unabsorbed 95 percent of EDTA that remains within the digestive tract, mixes with undigested food and nutrients while passing on out of the body in stool. This unabsorbed EDTA tightly binds to and blocks absorption of many essential nutritional trace

elements as it passes through, thereby potentially blocking the uptake of important nutrients such as zinc, manganese, chromium, vanadium, copper, chromium, molybdenum and other essential nutrients, causing deficiencies.

When a chelator such as EDTA enters the body, either by mouth or intravenously, it could possibly remove 10 to 20 times more of the essential nutritional trace elements (such as zinc and manganese) than it does the undesired heavy metals or toxins that are deleterious. When given intravenously, thus bypassing any absorption problems, a full therapeutic treatment of EDTA can be completed with 20 to 50 daily doses. The replenishment of the lost essential trace elements by dietary supplementation can then take place during the remaining 315+ days of the year after the treatment, when the exogenously administered chelating agent(s) such as EDTA have been excreted or eliminated, and are not present to interfere. Because such a small amount is absorbed by mouth, oral EDTA is often given every day, but for up to 20 times or more as long, to accumulate what is alleged to be an effective dose, and there is no interim opportunity to replenish the essential nutrients that are being continuously blocked and depleted during the chelation therapy.

Thus, the daily administration of chelating agents such as EDTA by mouth may cause progressive deficiencies of zinc, manganese and other essential trace nutrients, which are an essential part of the body's antioxidant defenses. For example, the activity of superoxide dismutase (SOD), a very important intracellular antioxidant, depends on zinc and manganese. By inactivating antioxidant enzymes, the daily intake of chelation agents by mouth may actually worsen the condition of the patients being treated.

Intravenous chelation therapy has been reported to stimulate the release of parathyroid hormone (parathormone) in a pulsatile manner, but orally administered chelation therapies, such as with EDTA, have not. Thus, if that mechanism of action is important to achieve the intended benefit, oral EDTA cannot achieve the goal.

Attempts have been reported to increase the amount of chelating agents that are used in an oral chelation therapy to match the levels that can be achieved when they are administered intravenously. However, there are many side effects that prevent this approach from being used.

### **3) Challenges with both oral and i.v. chelation therapies.**

The use of chelating agents for the removal of toxic heavy metals is based on their ability to form stable, nonionic, soluble and readily excretable complexes with the metal molecules in the tissues. They have proven valuable because they, in themselves, have a very low toxicity, are able to form soluble, excretable metal chelates within a body, and resist degradation by cell metabolites. However, the serious limitation for the use of chelating agents is that, when introduced into a body, they exist as hydrated anions in the blood plasma. These anions are unable to penetrate cellular membranes. Therefore, only extracellularly deposited toxic metals can be complexed by the chelating agents and removed from the body, whereas intracellularly deposited metals are not complexed by the chelating agent and therefore are not readily removed. Attempts have been made in the past to increase the penetration of

chelating agents through cellular membranes such as by the esterification of polyaminopolycarboxylic acids, but these efforts have met with limited success because of the insolubility and toxicity of the esterified compounds.

Thus, chelators such as EDTA typically remain extracellularly or outside of cells. By way of illustration, orally administered EDTA reaches only very low concentrations outside cell surfaces in the body and for brief periods of time, while intravenous infusions result in much higher levels, and can be maintained for several hours. However, intravenously administered EDTA can only chelate unwanted metals and toxins, if, e.g. they travel out of cell walls by diffusion. In contrast, this is not believed to occur to a significant extent – if at all – with chelators such as EDTA when taken by mouth. In sum, neither traditional approach achieves significant intracellular levels of chelating agents, and is thus unable to readily exert its actions intracellularly.

The preparations of the present invention comprise antioxidants that have effects that may be additive or synergistic to the effects of chelators such as EDTA; however, these antioxidants may be lipophilic. Because many parenterally suitable fluids such as saline, dextran, blood, stabilized hemoglobin solutions, etc., are all aqueous solutions, a problem with therapies based on lipid soluble antioxidants, such as .alpha.-lipoic acid, is the poor water solubility of these ingredients. The solubility may be enhanced by adding benzyl alcohol or DMSO, but such solvents introduce additional side effects.

Previous methods of delivering lipophilic antioxidants that involved solubilizing the antioxidant in solvents such as benzyl alcohol, DMSO, or other chemicals not only have the potential to introduce new toxicities, e.g. they may exacerbate microvascular injury, but the presence of these solvents confuses the interpretation of any protocol designed to evaluate antioxidant effects.

This invention provides novel solutions to these and other problems.

### **SUMMARY OF THE INVENTION**

It is an object of the present invention to provide a method for transferring at least two ingredients, comprising an antioxidant and a chelating agent, across a cellular membrane.

Another object of the present invention is to provide a means for introducing at least two ingredients, comprising an antioxidant and a chelating agent, into the interior of a cell.

It is another object of the present invention to provide a method for introducing at least two ingredients, comprising an antioxidant and a chelating agent, into the interior of a cell of a living organism by introducing the at least two ingredients to the organism and carrying it to the cell in the blood stream. In a preferred but non-limiting aspect, the at least two ingredients are introduced by oral administration.

Another object of the present invention is to provide a method for the removal of intracellularly deposited toxic heavy metals.

Still another object of the present invention is to provide a therapy method for toxic heavy metal poisoning whereby both intracellularly deposited toxic heavy metals as well as extracellularly deposited toxic heavy metals can be removed from the body. In separate aspect, said body is a human body or an animal body (e.g. a pet or other raised animal).

In one embodiment, this invention provides novel preparations comprised of the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

- a) one or more members selected from Group 1 (e.g. DIM); and
- b) one or more members selected from Group 2 (e.g. grape skin extract, resveratrol, and piceatannol).

In one embodiment, this invention provides novel preparations comprised of the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

- a) one or more members selected from Group 1 (e.g. DIM); and
- b) one or more members selected from Group 3 (e.g. calcium D-glucarate).

**In one embodiment, this invention provides novel preparations comprised of the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:**

- a) one or more members selected from Group 1 (e.g. DIM); and**
- b) one or more members selected from Group 4 (e.g. medium chain triglycerides).**

**In one embodiment, this invention provides novel preparations comprised of the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:**

- a) one or more members selected from Group 1 (e.g. DIM); and**
- b) one or more members selected from Group 5 (e.g. lecithin and phosphatidyl choline).**

**In one embodiment, this invention provides novel preparations comprised of the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:**

- a) one or more members selected from Group 2 (e.g. grape skin extract, resveratrol, and piceatannol); and**
- b) one or more members selected from Group 3 (e.g. calcium D-glutarate).**

**In one embodiment, this invention provides novel preparations comprised of the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:**

- a) one or more members selected from Group 2 (e.g. grape skin extract, resveratrol, and piceatannol); and
- b) one or more members selected from Group 4 (e.g. medium chain triglycerides).

In one embodiment, this invention provides novel preparations comprised of the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

- a) one or more members selected from Group 2 (e.g. grape skin extract, resveratrol, and piceatannol); and
- b) one or more members selected from Group 5 (e.g. lecithin and phosphatidyl choline).

In one embodiment, this invention provides novel preparations comprised of the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

- a) one or more members selected from Group 3 (e.g. calcium D-glutarate); and
- b) one or more members selected from Group 4 (e.g. medium chain triglycerides).

In one embodiment, this invention provides novel preparations comprised of the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

- a) one or more members selected from Group 3 (e.g. calcium D-glutarate); and
- b) one or more members selected from Group 5 (e.g. lecithin and phosphatidyl choline).



In one embodiment, this invention provides novel preparations comprised of the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

- a) one or more members selected from Group 4 (e.g. medium chain triglycerides); and
- b) one or more members selected from Group 5 (e.g. lecithin and phosphatidyl choline).

In one embodiment, this invention provides novel preparations comprised of the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

- a) one or more members selected from Group 1 (e.g. DIM);
- b) one or more members selected from Group 2 (e.g. grape skin extract, resveratrol, and piceatannol); and
- c) one or more members selected from Group 3 (e.g. calcium D-glucarate).

In one embodiment, this invention provides novel preparations comprised of the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

- a) one or more members selected from Group 1 (e.g. DIM);
- b) one or more members selected from Group 2 (e.g. grape skin extract, resveratrol, and piceatannol); and
- c) one or more members selected from Group 4 (e.g. medium chain triglycerides).

In one embodiment, this invention provides novel preparations comprised of the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

- a) one or more members selected from Group 1 (e.g. DIM);
- b) one or more members selected from Group 2 (e.g. grape skin extract, resveratrol, and piceatannol); and
- c) one or more members selected from Group 5 (e.g. lecithin and phosphatidyl choline).

In one embodiment, this invention provides novel preparations comprised of the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

- a) one or more members selected from Group 1 (e.g. DIM);
- b) one or more members selected from Group 3 (e.g. calcium D-glucarate); and
- c) one or more members selected from Group 4 (e.g. medium chain triglycerides).

In one embodiment, this invention provides novel preparations comprised of the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

- a) one or more members selected from Group 1 (e.g. DIM);
- b) one or more members selected from Group 3 (e.g. calcium D-glucarate); and
- c) one or more members selected from Group 5 (e.g. lecithin and phosphatidyl choline).

In one embodiment, this invention provides novel preparations comprised of the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

- a) one or more members selected from Group 1 (e.g. DIM);
- b) one or more members selected from Group 4 (e.g. medium chain triglycerides); and
- c) one or more members selected from Group 5 (e.g. lecithin and phosphatidyl choline).

In one embodiment, this invention provides novel preparations comprised of the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

- a) one or more members selected from Group 2 (e.g. grape skin extract, resveratrol, and piceatannol);
- b) one or more members selected from Group 3 (e.g. calcium D-glucarate); and
- c) one or more members selected from Group 4 (e.g. medium chain triglycerides).

In one embodiment, this invention provides novel preparations comprised of the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

- a) one or more members selected from Group 2 (e.g. grape skin extract, resveratrol, and piceatannol);
- b) one or more members selected from Group 3 (e.g. calcium D-glucarate); and
- c) one or more members selected from Group 5 (e.g. lecithin and phosphatidyl choline).

**In one embodiment, this invention provides novel preparations comprised of the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:**

- a) one or more members selected from Group 2 (e.g. grape skin extract, resveratrol, and piceatannol);**
- b) one or more members selected from Group 4 (e.g. medium chain triglycerides); and**
- c) one or more members selected from Group 5 (e.g. lecithin and phosphatidyl choline).**

**In one embodiment, this invention provides novel preparations comprised of the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:**

- a) one or more members selected from Group 3 (e.g. calcium D-glucarate);**
- b) one or more members selected from Group 4 (e.g. medium chain triglycerides); and**
- c) one or more members selected from Group 5 (e.g. lecithin and phosphatidyl choline).**

**In one embodiment, this invention provides novel preparations comprised of the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:**

- a) one or more members selected from Group 1 (e.g. DIM);**
- b) one or more members selected from Group 2 (e.g. grape skin extract, resveratrol, and piceatannol);**
- c) one or more members selected from Group 3 (e.g. calcium D-glucarate); and**
- d) one or more members selected from Group 4 (e.g. medium chain triglycerides).**

**In one embodiment, this invention provides novel preparations comprised of the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:**

- a) one or more members selected from Group 1 (e.g. DIM);**
- b) one or more members selected from Group 2 (e.g. grape skin extract, resveratrol, and piceatannol);**
- c) one or more members selected from Group 3 (e.g. calcium D-glucarate); and**
- d) one or more members selected from Group 5 (e.g. lecithin and phosphatidyl choline).**

**In one embodiment, this invention provides novel preparations comprised of the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:**

- a) one or more members selected from Group 1 (e.g. DIM);**
- b) one or more members selected from Group 2 (e.g. grape skin extract, resveratrol, and piceatannol);**
- c) one or more members selected from Group 4 (e.g. medium chain triglycerides); and**
- d) one or more members selected from Group 5 (e.g. lecithin and phosphatidyl choline).**

**In one embodiment, this invention provides novel preparations comprised of the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:**

- a) one or more members selected from Group 1 (e.g. DIM);**

- b) one or more members selected from Group 3 (e.g. calcium D-glucarate);
- c) one or more members selected from Group 4 (e.g. medium chain triglycerides); and
- d) one or more members selected from Group 5 (e.g. lecithin and phosphatidyl choline).

In one embodiment, this invention provides novel preparations comprised of the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

- a) one or more members selected from Group 1 (e.g. DIM);
- b) one or more members selected from Group 2 (e.g. grape skin extract, resveratrol, and piceatannol);
- c) one or more members selected from Group 3 (e.g. calcium D-glucarate);
- d) one or more members selected from Group 4 (e.g. medium chain triglycerides); and
- e) one or more members selected from Group 5 (e.g. lecithin and phosphatidyl choline).

According to this invention, the term "at least one member" in reference to inventive embodiments that are to be protected includes, minimally, every integer value from one to at 20, inclusive; i.e. in one aspect it means at least one member, in another aspect it means at least two members, in another aspect it means at least three members, ..., etc, and in another aspect it means at least 20 members.

In one embodiment, this invention provides every combination and permutation of ingredients exemplified in Table 1 (i.e. Groups A-G). In another embodiment, this invention

provides every combination and permutation of ingredients exemplified in from Table 3 (i.e. Groups 1-5).

In yet another embodiment, this invention provides every combination and permutation of ingredients selected from both Table 1 (i.e. Groups A-G) and Table 3 (Groups 1-5), particularly in a kit. For example, such a kit may have two preparations: 1) a preparation comprised of ingredients from Table 1; and 2) a preparation comprised of ingredients from Table 3; the two preparations may be physically separate; and, by way of non-limiting exemplification, the first preparation may be a liquid preparation that is consumed using a spoon, while the second preparation may be a preparation that is in the form of vegetable capsules (v-caps) that can be consumed like any capsule, tablet or pill.

In one embodiment, this invention provides a preparation of encapsulated bioavailable chelating agents comprised of the following ingredients:

- a) one or more members selected from a first group consisting of: R-(+)-.alpha.-lipoic acid (substantially enantiomerically pure), S-(-)-.alpha.-lipoic acid (substantially enantiomerically pure), R/S-.alpha.-lipoic acid (racemic mixture), R/S-.gamma.-lipoic acid (racemic mixture), other isomers of alpha lipoic acid, derivatives of alpha lipoic acid, dihydrolipoic acid (DHLLA); wherein at least 1% of said one or more members from said first group is in microspheres or liposomes; and
- b) one or more members selected from a second group consisting of: EDTA, EGTA, DPTA, TTHA, HEDHA, NOTA, DOTA, HEDTA, other polyaminopolycarboxylic acids, iminodiacetic acid (IDA), cyclam, penicillamine, dimercaptosuccinic acid, tartrate, thiomalic

acid, crown ethers, nitrilotriacetic acid (NTA), 3,6-dioxaoctanedithioamide, 3,6-dioxaoctanediamide, salicyladoximine, dithio-oxamide, 8-hydroxyquinoline, cupferron, 2,2'-thiobis(ethyl acetoacetate), 2,2'-dipyridyl; wherein at least 1% of said one or more members from said second group is in microspheres or liposomes; and

c) one or more members selected from a third group consisting of:

lecithin, phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine, dilinoleylphosphatidylcholine, lysolipids, dipalmitoylphosphatidylcholine, distearoylphosphatidylcholine, phosphatidylcholine, phosphatidic acid, sphingomyelin, cholesterol, cholesterol sulfate, cholesterol hemisuccinate, tocopherol hemisuccinate, phosphatidylethanolamine, phosphatidylinositol, palmitic acid, stearic acid, oleic acid, linolenic acid, linoleic acid; wherein at least 1% of said one or more members from said third group is in microspheres or liposomes.

This invention provides, in non-limiting embodiments, novel preparations of chelating agents encapsulated in micelles or liposomes comprising the triple combination of: 1) micelles or liposomes comprising alpha lipoic acid or a derivative thereof and 2) micelles or liposomes comprising a chelating agent, such as EDTA; and furthermore, in different embodiments, optionally 3) magnesium chloride. The micelles or liposomes may be comprised of what have been termed "essential phospholipids".



## **TERMS**

Biologically active and bioactive are used interchangeably, and can refer to in vitro as well as to in vivo situations.

Physiological solutions suitable for intravenous injection include: e.g. Saline. In lieu of normal saline, other pharmaceutically acceptable solutions may be utilized including, but not limited to, 0.9% saline solution, 5% dextrose solution, lactated Ringer's solution, 5% dextrose in lactated Ringer's solution, dextrose-saline combinations, albumin-containing solutions, dextran, dextran-saline combinations, etc.

POEBACA: preparation(s) of encapsulated bioavailable chelating agents(s). Both plural and singular meanings are included.

POEBACAI: ingredient(s) for making up (a) preparation(s) of encapsulated bioavailable chelating agents(s). POEBACAI can exist in encapsulated form or in nonencapsulated form (e.g. a pre-encapsulated stage). Both plural and singular meanings are included.

1 ounce (oz.) = 28.3495231 grams (gm)

128 ounces = 1 gallon

## **DETAILED DESCRIPTION OF THE INVENTION**

### **Ingredients.**

This invention provides novel preparations of encapsulated bioavailable chelating agents (POEBACA), wherein in each of different preferred embodiments a POEBACA is comprised of the following ingredients (or PEOBACA), for which non-limiting examples are listed in Table 1:

- a) one or more members selected from Group A (e.g. alpha lipoic acid);
- b) one or more members selected from Group B (e.g. EDTA);
- c) one or more members selected from Group C (e.g. lecithin);
- d) optionally, in separate embodiments, one or more members selected from Group D (e.g. magnesium chloride);
- e) optionally, in separate embodiments, one or more members selected from Group E (glutathione);
- f) optionally, in separate embodiments, one or more members selected from Group F (e.g. vinpocetine);
- g) optionally, in separate embodiments, one or more members selected from Group G (e.g. nitrogen gas);

wherein the ingredients are prepared in a manner that provides the encapsulation of a significant fraction of one or more ingredient(s) into liposomes or micropsheres.

This invention also provides novel preparations comprised of the following (optionally encapsulated) edible ingredients, for which non-limiting examples are listed in Table 3:

- a) one or more members selected from Group 1 (e.g. DIM);
- b) one or more members selected from Group 2 (e.g. grape skin extract, resveratrol, and piceatannol);
- c) one or more members selected from Group 3 (e.g. calcium D-glucarate);
- d) one or more members selected from Group 4 (e.g. medium chain triglycerides);
- e) optionally, in separate embodiments, one or more members selected from Group 5 (e.g. lecithin);

In one embodiment, this invention provides that a serviceable ingredient that is a member of Group 4, can be a preparation in which at least half of the content by weight is MCTs, said at least half of the content by weight of MCTs comprising at least about 40% MCTs having lengths between  $C_5$  and  $C_{11}$ . In separate embodiments, said at least half of the content by weight of MCTs can range from at least about 40% to at least about 95% (also including every integer value in this range) MCTs having lengths between  $C_5$  and  $C_{11}$ . Thus, for example, this invention provides that a serviceable ingredient that is a member of Group 4, can be a preparation in which at least half of the content by weight is MCTs, said at least half of the content by weight of MCTs comprising at least about 90% MCTs having lengths between  $C_5$  and  $C_{11}$ .

**Preferred numbers of Group A members (e.g. alpha lipoic acid).**

According to this invention, separate preferred embodiments of "preparations of encapsulated bioavailable chelating agents" (i.e. POEBACA) are provided herein, each of which is comprised of at least a minimum number of members, i.e. "n" member(s), selected from Group A, where  $n = 1, 2, 3, \dots, 100$ , including every integer value within the range of 1 to 100. Thus, there are at least 100 embodiments of POEBACA, differing in that the minimum number of members selected from Group A that is contained in each embodiment ranges from one to one hundred (including every integer value in between), i.e. at least one, at least two, at least three, at least four, ..., and up to at least 100. Thus, one preferred embodiment of this invention provides a POEBACA comprised of at least one member selected from Group A; another preferred embodiment of this invention provides a POEBACA comprised of at least two members selected from Group A; another preferred embodiment of this invention provides a POEBACA comprised of at least three members selected from Group A; etc. ; another preferred embodiment of this invention provides a POEBACA comprised of at least one hundred members selected from Group A; for convenience these are referred to as preferred embodiments A1 to A100, and these separate embodiments are intended to be the subject matter of separate claims according to this invention.

**Preferred numbers of Group B members (e.g. EDTA).**

According to this invention, separate preferred embodiments of "preparations of encapsulated bioavailable chelating agents" (i.e. POEBACA) are provided herein, each of which is comprised of at least a minimum number of members, i.e. "n" member(s), selected

from Group B, where  $n = 1, 2, 3, \dots, 100$ , including every integer value within the range of 1 to 100. Thus, there are at least 100 embodiments of POEBACA, differing in that the minimum number of members selected from Group B that is contained in each embodiment ranges from one to one hundred (including every integer value in between), i.e. at least one, at least two, at least three, at least four, ..., and up to at least 100. Thus, one preferred embodiment of this invention provides a POEBACA comprised of at least one member selected from Group B; another preferred embodiment of this invention provides a POEBACA comprised of at least two members selected from Group B; another preferred embodiment of this invention provides a POEBACA comprised of at least three members selected from Group B; etc. ; another preferred embodiment of this invention provides a POEBACA comprised of at least one hundred members selected from Group B; for convenience these are referred to as preferred embodiments B1 to B100, and these separate embodiments are intended to be the subject matter of separate claims according to this invention.

**Preferred numbers of Group C members (e.g. lecithin).**

According to this invention, separate preferred embodiments of "preparations of encapsulated bioavailable chelating agents" (i.e. POEBACA) are provided herein, each of which is comprised of at least a minimum number of members, i.e. "n" member(s), selected from Group C, where  $n = 1, 2, 3, \dots, 100$ , including every integer value within the range of 1 to 100. Thus, there are at least 100 embodiments of POEBACA, differing in that the minimum number of members selected from Group C that is contained in each embodiment

ranges from one to one hundred (with every integer value in between), i.e. at least one, at least two, at least three, at least four, ..., and up to at least 100. Thus, one preferred embodiment of this invention provides a POEBACA comprised of at least one member selected from Group C; another preferred embodiment of this invention provides a POEBACA comprised of at least two members selected from Group C; another preferred embodiment of this invention provides a POEBACA comprised of at least three members selected from Group C; etc. ; another preferred embodiment of this invention provides a POEBACA comprised of at least one hundred members selected from Group C; for convenience these are referred to as preferred embodiments C1 to 100, and these separate embodiments are intended to be the subject matter of separate claims according to this invention.

**Preferred numbers of Group D members (e.g. magnesium chloride).**

According to this invention, separate preferred embodiments of "preparations of encapsulated bioavailable chelating agents" (i.e. POEBACA) are provided herein, each of which is comprised of at least a minimum number of members, i.e. "n" member(s), selected from Group D, where  $n = 1, 2, 3, \dots, 20$ , including every integer value within the range of 1 to 20. Thus, there are at least 20 embodiments of POEBACA, differing in that the minimum number of members selected from Group D that is contained in each embodiment ranges from one to twenty (including every integer value in between), i.e. at least one, at least two, at least three, at least four, ..., and up to at least 20. Thus, one preferred embodiment of this invention provides a POEBACA comprised of at least one member selected from Group D;

another preferred embodiment of this invention provides a POEBACA comprised of at least two members selected from Group D; another preferred embodiment of this invention provides a POEBACA comprised of at least three members selected from Group D; etc. ; another preferred embodiment of this invention provides a POEBACA comprised of at least twenty members selected from Group D; for convenience these are referred to as preferred embodiments D1 to D20, and these separate embodiments are intended to be the subject matter of separate claims according to this invention.

**Preferred numbers of Group E members (e.g. glutathione).**

According to this invention, separate preferred embodiments of "preparations of encapsulated bioavailable chelating agents" (i.e. POEBACA) are provided herein, each of which is comprised of at least a minimum number of members, i.e. "n" member(s), selected from Group E, where  $n = 1, 2, 3, \dots, 20$ , including every integer value within the range of 1 to 20. Thus, there are at least 20 embodiments of POEBACA, differing in that the minimum number of members selected from Group E that is contained in each embodiment ranges from one to twenty (including every integer value in between), i.e. at least one, at least two, at least three, at least four, ..., and up to at least 20. Thus, one preferred embodiment of this invention provides a POEBACA comprised of at least one member selected from Group E; another preferred embodiment of this invention provides a POEBACA comprised of at least two members selected from Group E; another preferred embodiment of this invention provides a POEBACA comprised of at least three members selected from Group E; etc. ; another preferred embodiment of this invention provides a POEBACA comprised of at least

twenty members selected from Group E; for convenience these are referred to as preferred embodiments E1 to E20, and are intended to be claimed subject matter according to this invention.

**Preferred numbers of Group F members (e.g. vinpocetine).**

According to this invention, separate preferred embodiments of "preparations of encapsulated bioavailable chelating agents" (i.e. POEBACA) are provided herein, each of which is comprised of at least a minimum number of members, i.e. "n" member(s), selected from Group F, where  $n = 1, 2, 3, \dots, 20$ , including every integer value within the range of 1 to 20. Thus, there are at least 20 embodiments of POEBACA, differing in that the minimum number of members selected from Group F that is contained in each embodiment ranges from one to twenty (including every integer value in between), i.e. at least one, at least two, at least three, at least four, ..., and up to at least 20. Thus, one preferred embodiment of this invention provides a POEBACA comprised of at least one member selected from Group F; another preferred embodiment of this invention provides a POEBACA comprised of at least two members selected from Group F; another preferred embodiment of this invention provides a POEBACA comprised of at least three members selected from Group F; etc. ; another preferred embodiment of this invention provides a POEBACA comprised of at least twenty members selected from Group F; for convenience these are referred to as preferred embodiments F1 to F20, and these separate embodiments are intended to be the subject matter of separate claims according to this invention.



**Preferred numbers of Group G members (e.g. nitrogen gas).**

According to this invention, separate preferred embodiments of "preparations of encapsulated bioavailable chelating agents" (i.e. POEBACA) are provided herein, each of which is comprised of at least a minimum number of members, i.e. "n" member(s), selected from Group G, where  $n = 1, 2, 3, \dots, 20$ , including every integer value within the range of 1 to 20. Thus, there are at least 20 embodiments of POEBACA, differing in that the minimum number of members selected from Group G that is contained in each embodiment ranges from one to twenty (including every integer value in between), i.e. at least one, at least two, at least three, at least four, ..., and up to at least 20. Thus, one preferred embodiment of this invention provides a POEBACA comprised of at least one member selected from Group G; another preferred embodiment of this invention provides a POEBACA comprised of at least two members selected from Group G; another preferred embodiment of this invention provides a POEBACA comprised of at least three members selected from Group G; etc. ; another preferred embodiment of this invention provides a POEBACA comprised of at least twenty members selected from Group G; for convenience these are referred to as preferred embodiments G1 to G20, and these separate embodiments are intended to be the subject matter of separate claims according to this invention.

**Preferred numbers of members from Groups A through G.**

This invention further provides the additional preferred aspects that result from all the possible combinations and permutations of the preferred embodiments of A1 to A100, B1 to

B100, C1 to C100, D1 to D20, E1 to E20, F1 to F20, and G1 to G20. By way of illustration, (100 preferred embodiments corresponding to A1 to A100) x (100 preferred embodiments corresponding to B1 to B100) x (100 preferred embodiments corresponding to C1 to C100) x (20 preferred embodiments corresponding to D1 to D20) x (20 preferred embodiments corresponding to E1 to E20) x (20 preferred embodiments corresponding to F1 to F100) x (100 preferred embodiments corresponding to G1 to G20) = 160,000,000,000 or one hundred and sixty billion preferred aspects, and these separate aspects are intended to be the subject matter of separate claims according to this invention.

**Preferred amounts of ingredients.**

Furthermore, the relative amounts of each ingredient that can comprise a POEBACA according to this invention are illustrated in Table 2. In separate embodiments, this invention provides all the physically possible combinations and permutations of ingredient amounts that listed in Table 2. Thus, this invention provides that the relative amounts of these ingredients can vary (as illustrated in Table 2), yielding additional aspects. Therefore, when considering the claim limitations regarding the relative amount of ingredients, the number of preferred embodiments is greater, by orders of magnitude, than 160,000,000,000 or one hundred and sixty billion preferred embodiments that don't specify amounts of ingredients, and all these preferred embodiments are intended to be the subject matter of separate claims according to this invention.

**Table 1 Ingredients to be protected as claimed by this invention.**

<b>Group</b>	<b>Group Members (Non-limiting examples are listed for each group)</b>
<b>A</b>	<u>Antioxidants and hydrophobic ingredients</u> R-(+)-.alpha.-lipoic acid (substantially enantiomerically pure), S-(-)-.alpha.-lipoic acid (substantially enantiomerically pure), R/S-.alpha.-lipoic acid (racemic mixture), R/S-.gamma.-lipoic acid (racemic mixture), other isomers of alpha lipoic acid, derivatives of alpha lipoic acid (such as the dihydro version of these alpha lipoic acid isomers, also known as dihydrolipoic acid or DHLA), animal and vegetable oils, hydrocarbon oils, ester oils, silicone oils, higher fatty acids, higher alcohols, sunscreens agents, vitamins, ferulic acid
<b>B</b>	<u>Chelators</u> EDTA, EGTA, DPTA, TTHA, HEDHA, NOTA, DOTA, HEDTA, other polyaminopolycarboxylic acids, iminodiacetic acid (IDA), cyclam, penicillamine, dimercaptosuccinic acid, tartrate, thiomalic acid, crown ethers, nitrilotriacetate (NTA), 3,6-dioxaoctanedithioamide, 3,6-dioxaoctanediamide, salicyladoximine, dithio-oxamide, 8-hydroxyquinoline, cupferron, 2,2'-thiobis(ethyl acetoacetate), 2,2'-dipyridyl, and derivatives thereof
<b>C</b>	<u>Phospholipids, lipids and fatty acids</u> lecithin, phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine, dilinoleylphosphatidylcholine, lysolipids, dipalmitoylphosphatidylcholine, distearoylphosphatidylcholine, phosphatidylcholine, phosphatidic acid, sphingomyelin, cholesterol, cholesterol sulfate, cholesterol hemisuccinate, tocopherol hemisuccinate, phosphatidylethanolamine, phosphatidylinositol, fatty acids (e.g. palmitic acid, stearic acid, oleic acid, linolenic acid, linoleic acid, etc.), glycosphingolipids, glucolipids, glycolipids, sulphatides, lipids bearing sulfonated mono-, di-, oligo- or polysaccharides, lipids with ether and ester-linked fatty acids, triglycerides, lipoproteins (high or low density), cholesterol, and other lipids and polymerized lipids.
<b>D</b>	<u>Magnesium Salts</u> Magnesium chloride, Magnesium Gluconate, Magnesium Carbonate, Calcium Magnesium Citrate, Magnesium Sulfate
<b>E</b>	<u>Sulfur-Containing Amino Acids, Sulfur-Containing Peptides, Sulfur-Containing Proteins</u> Glutathione, methionine, cysteine
<b>F</b>	Plant alkaloids (e.g. vinpocetine, vincamine), coenzyme Q10, and analogues coenzyme Q10 (e.g. idebenone)
<b>G</b>	<u>Gaseous ingredient</u> Nitrogen gas, oxygen gas, atmospheric air, gaseous mixtures containing nitrogen gas, gaseous mixtures containing oxygen gas.

**Table 2. Amounts of ingredients to be protected as claimed by this invention. Values are normalized to 2 oz or approximately 56 grams.**

Group (with example of a group member)	Example 1 (Absolute amount, mg)	Example 1 (Relative amount, %)	Preferred amounts intended for protection according to this invention (both individually and collectively as a group)
A (e.g. alpha lipoic acid)	100.0 mg	0.17	From about 0.01 mg to about 20,000 mg inclusive, including specifically each increment of about 0.01 mg within this range.
B (e.g. EDTA)	1,000.0 mg	1.7	From about 0.01 mg to about 30,000 mg inclusive, including specifically each increment of about 0.01 mg within this range.
C (e.g. lecithin)	30,000.0 mg	50.0	From about 0.01 mg to about 40,000 mg inclusive, including specifically each increment of about 0.01 mg within this range.
D (e.g. magnesium chloride)	150.0 mg	0.26	From about 0.01 mg to about 10,000 mg inclusive, including specifically each increment of about 0.01 mg within this range.
E (e.g. glutathione)	1,000mg	1.7	From about 0.01 mg to about 10,000 mg inclusive, including specifically each increment of about 0.01 mg within this range.
F (e.g. vinpocetine)	100 mg	0.17	From about 0.01 mg to about 10,000 mg inclusive, including specifically each increment of about 0.01 mg within this range.
<b>Example 1.</b> Other ingredients: Water (30 – 40%), Ethanol (5 – 15 %), Gum Arabic (0.5 – 2%), Flavorings (0 – 5 %).			

**Table 3 Ingredients to be protected as claimed by this invention.**

(See Table 4 for preferred amounts according to this invention)

Group	Group Members (Non-limiting examples are listed for each group)
1	<p><u>Plant indoles, including sources of plant indoles (e.g. DIM).</u></p> <p>Sources of plant indoles include including vegetables, as well as parts thereof (e.g. skin, flesh, seeds, etc.) and extracts thereof (e.g. skin extracts), belonging to or related to the mustard family (Cruciferae or Brassicaceae), which includes the alyssum, candytuft, cabbage, radish, broccoli, and many weeds. DIM is also found in grapes, teas (e.g. black teas), cranberry, cherries, blackberries and other berries.</p> <p>E.g. Indole-3-carbinol (I3C) and its dimer 3,3'-diindolylmethane (DIM). It is appreciated that substances such as I3C and DIM can be modified or derivatized (form a chemical point of view), and both the alternative use of and the additional use of these modified or derivatized substances are also protected by this invention.</p>
2	<p><u>Plant flavonoids, polyphenols, stilbenes and related substances (PFPSARS), including sources of plant flavonoids, polyphenols, stilbenes, and related substances (e.g. 3,5,4'-trihydroxy stilbene or resveratrol, piceatannol, and grape skin extract).</u></p> <p>Sources of plant polyphenols include at least 70 to 80 species (if not a lot more), e.g. mulberries, peanuts, and grapes, as well as parts thereof (e.g. skin, flesh, seeds, etc.) and extracts thereof (e.g. skin extracts such as curcumin skin extract and grape skin extract), as well as in wines and vinegars. PFPSARS are also found, by way of non-limiting examples, in a) <u>Piper methysticum</u>, kava kava, Piperaceae, plant in flower; b) <u>Pinus resinosa</u>, red pine, Pinaceae, trees in forest; c) <u>Saccharum officinarum</u>, sugar cane, Poaceae, drawing; d) <u>Vitis vinifera</u>, grape, Vitaceae, fruits; <u>Morus alba</u>, mulberry, Moraceae, male and female flowers; e) <u>Marchantia polymorpha</u>, a liverwort, gametophytes and sporophytes; f) <u>Orchis militaris</u>, Helm Knabenkraut, Orchidaceae, flowers; and g) huzhang (<u>Polygonum cuspidatum</u> aka "tiger cane" or giant knotweed).</p> <p>E.g. Resveratrol and its metabolite piceatannol. It is appreciated that substances such as resveratrol and piceatannol can be modified or derivatized (form a chemical point of view), and both the alternative use of and the additional use of these modified or derivatized substances are also protected by this invention.</p>

Group	Group Members (Non-limiting examples are listed for each group)
3	<p data-bbox="418 394 1304 457"><u>Glucaric acid and derivatives thereof (e.g. calcium d-glucarate and 1,4-GL) including sources thereof.</u></p> <p data-bbox="418 489 1341 552">Calcium D-glucarate is the calcium salt of D-glucaric acid, a natural substance found in many fruits and vegetables.</p> <p data-bbox="418 583 1360 772">It is appreciated that different salt of D-glucaric acid exist (e.g. potassium hydrogen D-glucarate or PHG), and that D-glucaric acid can be modified or derivatized (from a chemical point of view), and both the alternative use of and the additional use of these different salts or derivatized substances (e.g. D-glucaro-1,4-lactone or 1,4-GL, 2-keto-3-deoxy-D-glucarate, and 4-deoxy-5-keto-D-glucarate) are also protected by this invention.</p>
4	<p data-bbox="418 804 1356 888"><u>Medium Chain Triglycerides and sources thereof (e.g. a preparation in which at least half of the content by weight is MCT, said at least half of the content comprising at least 80% between C<sub>8</sub> and C<sub>12</sub> MCTs).</u></p> <p data-bbox="418 919 1292 1014">Sources of medium chain triglycerides or MCTs include coconut oil, palm kernel oil, camphor tree drupes, and butter. MCT are also available as a supplement.</p> <p data-bbox="418 1045 1356 1560">Medium chain triglycerides are medium-chain fatty acid esters of glycerol. Medium-chain fatty acids are fatty acids containing from six to 12 carbon atoms. Coconut and palm kernel oils are also called lauric oils because of their high content of the 12 carbon fatty acid, lauric or dodecanoic acid. Medium-chain triglycerides used for nutritional and other commercial purposes are sometimes derived from lauric oils. In the process of producing MCTs, lauric oils are hydrolyzed to medium-chain fatty acids and glycerol. The glycerol is drawn off from the resultant mixture, and the medium-chain fatty acids are fractionally distilled. The medium-chain fatty acid fraction used commercially is sometimes mainly comprised of the eight carbon caprylic or octanoic acid and the 10 carbon capric or decanoic acid. There are much smaller amounts of the six carbon caproic or hexanoic acid and the 12 carbon lauric acid in the commercial products. The caprylic- and capric-rich mixture is finally re-esterified to glycerol to produce medium-chain triglycerides that are mainly glycerol esters of caproic (C<sub>6</sub>) caprylic (C<sub>8</sub>), capric (C<sub>10</sub>) and lauric acid (C<sub>12</sub>) in a ratio of approximately 2:55:42:1. MCTs are represented by the following chemical structures:</p>

Group	Group Members (Non-limiting examples are listed for each group)
5	<p data-bbox="418 394 987 426"><u>Phospholipids and sources thereof (e.g. lecithin)</u></p> <p data-bbox="418 457 1356 793">Examples include lecithin, phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine, dilinoleylphosphatidylcholine, lysolipids, dipalmitoylphosphatidylcholine, distearoylphosphatidylcholine, phosphatidylcholine, phosphatidic acid, sphingomyelin, cholesterol, cholesterol sulfate, cholesterol hemisuccinate, tocopherol hemisuccinate, phosphatidylethanolamine, phosphatidylinositol, fatty acids (e.g. palmitic acid, stearic acid, oleic acid, linolenic acid, linoleic acid, etc.), glycosphingolipids, glucolipids, glycolipids, sulphatides, lipids bearing sulfonated mono-, di-, oligo- or polysaccharides, lipids with ether and ester-linked fatty acids, triglycerides, lipoproteins (high or low density), cholesterol, and other lipids and polymerized lipids.</p>

**Table 4. Amounts of ingredients to be protected as claimed by this invention. Values are normalized to a “00” capsule, containing approximately 800 mg total (typically in the range of approximately 700 – 900 mg).**

Group (with example of a group member)	Example 4 (Absolute amount, mg)	Example 4 (Relative amount, %, assuming approx. 800 mg total)	Preferred amounts intended for protection as claimed according to this invention (both individually and collectively as a group)
1 (e.g. DIM)	100 mg	12.5	From about 0.01 mg to about 600 mg inclusive, including specifically each increment of about 0.01 mg within this range.
2 (e.g. Grape skin extract and resveratrol)	200 mg	25.0	From about 0.01 mg to about 600 mg inclusive, including specifically each increment of about 0.01 mg within this range.
3 (e.g. calcium D-Glucarate)	200 mg	25.0	From about 0.01 mg to about 600 mg inclusive, including specifically each increment of about 0.01 mg within this range.
4 (e.g. medium chain triglycerides)	50 mg	6.25	From about 0.01 mg to about 600 mg inclusive, including specifically each increment of about 0.01 mg within this range.
5 (e.g. lecithin and phosphatidyl)	50mg	6.25	From about 0.01 mg to about 600 mg inclusive, including specifically each increment of about 0.01 mg within this range.
<b>Example 4.</b> Other optional ingredients: Cellulose powder (1-20%), Magnesium silicate (1 – 20 %), Magnesium stearate (0.1 -10%), Silicon dioxide (0.1-10%), Gum Acacia (0.1-10%), Other flavorings (0 – 10 %).			



This invention provides that the instant preparations comprising ingredients exemplified in Table 1 are preferably orally ingestible. In a non-limiting exemplification these preparations can be liquids (e.g. that can be orally ingested with the help of a spoon), or capsules, tablets, and pills. In non-limiting exemplifications, they can also be formed into flavored bars (e.g. similar to what bars that are marketed as "power bars", "diet bars", "energy bars", and "nutritional bars").

This invention provides that the instant preparations comprising ingredients exemplified in Table 3 are preferably orally ingestible. In a non-limiting exemplification these preparations can be liquids (e.g. that can be orally ingested with the help of a spoon), or capsules, tablets, and pills. In non-limiting exemplifications, they can also be formed into flavored bars (e.g. similar to what bars that are marketed as "power bars", "diet bars", "energy bars", and "nutritional bars").

This invention provides that the ingredients required herein, such as the ingredients exemplified in Table 1 and in Table 3 (for making the instant preparations) are ingredients that are commercially available from numerous commercial sources.

In Table 2 the relative amounts of each ingredient (POEBACAI) have been expressed in the context of a 2 ounce dose. This is for convenience and consistency, but in separate embodiments this invention provides that that dosages or other sizes can be prepared and administered, particularly ranging, by way of non-limiting exemplification, from about 0.1 ounce to about 128 ounces (or one gallon), including every 0.1 ounce increment in between.

**Preferred amount(s) of Group A members (e.g. alpha lipoic acid).**

This invention provides separate embodiments wherein per 2 ounces the total amount of ingredient(s) from Group A (e.g. alpha lipoic acid) collectively is preferably from about 0.01 mg to about 20,000 mg inclusive, including specifically each increment of about 0.01 mg within this range. Furthermore, this invention provides separate embodiments wherein per 2 ounces the total amount of each specific Group A ingredient(s) individually is preferably from about 0.01 mg to about 20,000 mg inclusive, including specifically each increment of about 0.01 mg within this range.

Thus; by way of illustration:

- 1) in one embodiment, this invention provides preparations of encapsulated bioavailable chelating agents (i.e. POEBACA) wherein the total amount of Group A members (e.g. alpha lipoic acid) is preferably 0.01 mg;
  - 2) in another embodiment, this invention provides preparations of encapsulated bioavailable chelating agents (i.e. POEBACA) wherein the total amount of Group A members (e.g. alpha lipoic acid) is preferably 0.02 mg;
  - 3) in another embodiment, this invention provides preparations of encapsulated bioavailable chelating agents (i.e. POEBACA) wherein the total amount of Group A members (e.g. alpha lipoic acid) is preferably 0.03 mg; etc. ;
- and

2,000,000) in another embodiment, this invention provides preparations of encapsulated bioavailable chelating agents (i.e. POEBACA) wherein the total amount of Group A members (e.g. alpha lipoic acid) is preferably 20,000 mg.

Thus, there are at least 2,000,000 preferred embodiments. This is illustrated in Table 2.

**Preferred amount(s) of Group B members (e.g. EDTA).**

This invention provides separate embodiments wherein per 2 ounces the total amount of ingredient(s) from Group B (e.g. EDTA) collectively is preferably from about 0.01 mg to about 30,000 mg inclusive, including specifically each increment of about 0.01 mg within this range. Furthermore, this invention provides separate embodiments wherein per 2 ounces the total amount of each specific Group B ingredient(s) individually is preferably from about 0.01 mg to about 30,000 mg inclusive, including specifically each increment of about 0.01 mg within this range.

**Preferred amount(s) of Group C members (e.g. lecithin).**

This invention provides separate embodiments wherein per 2 ounces the total amount of ingredient(s) from Group C (e.g. lecithin) collectively is preferably from about 0.01 mg to about 40,000 mg inclusive, including specifically each increment of about 0.01 mg within this range. Furthermore, this invention provides separate embodiments wherein per 2 fluid ounces the total amount of each specific Group C ingredient(s) individually is preferably from about 0.01 mg to about 40,000 mg inclusive, including specifically each increment of about 0.01 mg within this range.

**Preferred amount(s) of Group D members (e.g. magnesium chloride).**

This invention provides separate embodiments wherein per 2 ounces the total amount of ingredient(s) from Group D (e.g. magnesium chloride) collectively is preferably from about 0.01 mg to about 10,000 mg inclusive, including specifically each increment of about 0.01 mg within this range. Furthermore, this invention provides separate embodiments wherein per 2 ounces the total amount of each specific Group D ingredient(s) individually is preferably from about 0.01 mg to about 10,000 mg inclusive, including specifically each increment of about 0.01 mg within this range.

**Preferred amount(s) of Group E members (e.g. glutathione).**

This invention provides separate embodiments wherein per 2 ounces the total amount of ingredient(s) from Group E (e.g. glutathione) collectively is preferably from about 0.01 mg to about 10,000 mg inclusive, including specifically each increment of about 0.01 mg within this range. Furthermore, this invention provides separate embodiments wherein per 2 fluid ounces the total amount of each specific Group E ingredient(s) individually is preferably from about 0.01 mg to about 10,000 mg inclusive, including specifically each increment of about 0.01 mg within this range.

**Preferred amount(s) of Group F members (e.g. vinpocetine).**

This invention provides separate embodiments wherein per 2 ounces the total amount of ingredient(s) from Group F (e.g. vinpocetine) collectively is preferably from about 0.01 mg to about 10,000 mg inclusive, including specifically each increment of about 0.01 mg within

this range. Furthermore, this invention provides separate embodiments wherein per 2 ounces the total amount of each specific Group F ingredient(s) individually is preferably from about 0.01 mg to about 10,000 mg inclusive, including specifically each increment of about 0.01 mg within this range.

**Preferred percentages of encapsulated Group G members (e.g. nitrogen gas).**

This invention provides separate embodiments wherein one or more gases may be contained in a percentage of the liposomes or micropsheres in a POEBACA. In separate embodiments, the percent of liposomes or micropsheres that contains a gas is from about 1% to about 100%, including every integer value in between.

**Preferred methods of administration.**

This invention provides POEBACA that can be administered by several routes, including intravenous, topical, and oral. Furthermore, in separate embodiments, this invention provides forms of POEBACA that can be administered by inoculation or injection, (e.g., intraperitoneal, intramuscular, subcutaneous, intra-aural, intra-articular, intra-mammary, etc.), topical application (e.g., on areas, such as eyes, ears, skin or on afflictions such as wounds, burns, etc.), and by absorption through epithelial or mucocutaneous linings (e.g. vaginal and other epithelial linings, gastrointestinal mucosa, etc.). Methods are known for making POEBACA containing liposomes that are suitable for each of these methods of administration as well as other methods of administration that are known in the art.

For example, in preferred embodiments, this invention provides POEBACA in liquid forms that can be administered orally. The POEBACA can be also prepared as capsules, tablets,

pellets (e.g. for animal consumption), suppositories, or creams and ointments. The POEBACA can be also prepared as physiological solutions suitable for i.v. administration or other parenteral administration.

In as many separate aspects, this invention also provides all the possible combinations of ingredient quantities that are possible (e.g. the total of all the ingredients or POEBACAI does not surpass 100% of the relevant total dosage of the POEBACA, and admixing or solubility limitations are not exceeded).

**Preferred percentages of ingredients that are contained in liposomes or micropsheres.**

In separate aspects, this invention also provides that a POEBACA may include ingredients (or POEBACAI) that are not contained in micropsheres or liposomes in addition to ingredients that are contained in liposomes, and that these ingredients may be the same or different substances.

In separate aspects, this invention also provides that for each ingredient (or POEBACAI) the percent that is contained in micropsheres or liposomes (in contrast to the percentage that is not contained in micropsheres or liposomes, but rather is in solution) may be from about 0.1% to about 100.0%, including every 0.1% increment within this range. This provides at least about 1000 separate aspects that are intended for protection according to this invention.

In separate aspects, this invention also provides that in a single POEBACA, the microspheres or liposomes may be fairly homogeneous in size or in content; alternatively they may be fairly heterogeneous in size or in content.

**Preferred Group A members (e.g. alpha lipoic acid).**

Group A members include: antioxidants, particularly hydrophobic antioxidants and other hydrophobic ingredients.

Group A members include, but are not limited to:

R-(+)-.alpha.-lipoic acid (substantially enantiomerically pure), S-(-)-.alpha.-lipoic acid (substantially enantiomerically pure), R/S-.alpha.-lipoic acid (racemic mixture), R/S-.gamma.-lipoic acid (racemic mixture), other isomers of alpha lipoic acid, derivatives of alpha lipoic acid (such as the dihydro version of these alpha lipoic acid isomers, also known as dihydrolipoic acid or DHLA), animal and vegetable oils, hydrocarbon oils, ester oils, silicone oils, higher fatty acids, higher alcohols, sunscreens agents, vitamins, ferulic acid.

Group A members also include, but are not limited to:

fatty acids, lysolipids, dipalmitoylphosphatidylcholine, distearoylphosphatidylcholine, phosphatidylcholine, phosphatidic acid, sphingomyelin, cholesterol, cholesterol sulfate, cholesterol hemisuccinate, tocopherol hemisuccinate, phosphatidylethanolamine, phosphatidylinositol, glycosphingolipids, glucolipids, glycolipids, sulphatides, lipids bearing sulfonated mono-, di-, oligo- or polysaccharides, lipids with ether and ester-linked fatty acids, and polymerized lipids.

**Preferred Group B members (e.g. EDTA).**

Group B members include: chelators or chelating agents.

Group B members include, but are not limited to:

EDTA, EGTA, DPTA, TTHA, HEDHA, NOTA, DOTA, HEDTA, other polyaminopolycarboxylic acids, iminodiacetic acid (IDA), cyclam, penicillamine, dimercaptosuccinic acid, tartrate, thiomalic acid, crown ethers, nitrilotriacetic acid (NTA), 3,6-dioxaoctanedithioamide, 3,6-dioxaoctanediamide, salicyladoximine, dithio-oxamide, 8-hydroxyquinoline, cupferron, 2,2'-thiobis( ethyl acetoacetate), 2,2'-dipyridyl, and derivatives thereof. According to this invention, other chelators that are members of Group B are provided herein or are otherwise known in the art and can serve as ingredients for this invention.

**Preferred Group C members (e.g. lecithin).**

Group C members include: phospholipids, lipids and fatty acids.

Group C members include, but are not limited to:

lecithin, phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine, dilinoleylphosphatidylcholine, lysolipids, dipalmitoylphosphatidylcholine, distearoylphosphatidylcholine, phosphatidylcholine, phosphatidic acid, sphingomyelin, cholesterol, cholesterol sulfate, cholesterol hemisuccinate, tocopherol hemisuccinate, phosphatidylethanolamine, phosphatidylinositol, fatty acids (e.g. palmitic acid, stearic acid, oleic acid, linolenic acid, linoleic acid, etc.), glycosphingolipids, glucolipids, glycolipids, sulphatides, lipids bearing sulfonated mono-, di-, oligo- or polysaccharides, lipids with ether



and ester-linked fatty acids, triglycerides, lipoproteins (high or low density), cholesterol, and other lipids and polymerized lipids.

**Preferred Group D members (e.g. magnesium chloride).**

Group D members include: magnesium salts.

Group D members include, but are not limited to:

magnesium chloride, magnesium gluconate, magnesium carbonate, calcium magnesium citrate, magnesium sulfate, other salts of magnesium, and other forms of magnesium.

**Preferred Group E embers (e.g. glutathione).**

Group E embers include: sulfur-containing amino acids, sulfur-containing peptides, sulfur-containing proteins, and other sulfur-containing substances.

Group E members include, but are not limited to:

magnesium chloride, magnesium gluconate, magnesium carbonate, calcium magnesium citrate, magnesium sulfate, other salts of magnesium, and other forms of magnesium

**Preferred Group F members (e.g. vinpocetine).**

Group F members include: Vinpocetine, vincamine, idebenone

**Preferred Group G members (e.g. nitrogen gas).**

Group G members include: Nitrogen gas, atmospheric air, and other mixtures of gases that contain nitrogen, oxygen, mixtures of gases that contain oxygen, argon, and mixtures of gases that contain argon, etc.

**Lipophilic Anti-oxidants (e.g. alpha lipoic acid).** Alpha-lipoic acid, in addition to its non-toxicity and lipophilicity, has the advantage of being rapidly converted in tissues into its reduced form, dihydrolipoic acid (DHLA). DHLA also has potent antioxidant effects. Further, both .alpha.-lipoic acid and DHLA have been shown to disarm oxidants through a variety of mechanisms including free radical quenching, metal chelation, and regeneration of other common natural antioxidants.

In one embodiment, the present invention provides a lipophilic antioxidant in an aqueous physiological fluid, such as a resuscitation fluid by lipid encapsulation, e.g. by providing liposomal formation methods to form stable micellular solutions of .alpha.-lipoic acid or other lipophilic antioxidant(s).

The present invention seeks to overcome previous limitations by solubilizing .alpha.-lipoic acid in aqueous solution without the use of solvents such as harsh organic solvents. .alpha.-lipoic acid and other antioxidants are rendered soluble in aqueous solutions by the use of liposomal formation processes, such as ultrasonication. Because the .alpha.-lipoic molecule contains a polar (water soluble) carboxy-acid group and a non-polar, lipid soluble chain of carbon and sulfur atoms, the molecule is amphipathic, i.e., it has the ability to form micelles. Micelles may be formed in aqueous solution if a molecule possesses both polar and non-polar

groups. After ultrasonication the polar, a number of the water soluble ends of the .alpha.-lipoic acid molecule are on the outside of aggregations of .alpha.-lipoic acid. A number of the non-polar, lipid soluble tails are directed inward forming a tiny droplet, a micelle, which is water soluble. Ultrasonication of amphipathic molecules into micelles such as can be done with .alpha.-lipoic acid also has the possibility of creating mixed micelles. In this manner a mixture of .alpha.-lipoic acid with other antioxidants, which may not have the ability to form micelles alone for lack of any polar group, can be contained within a micelle of .alpha.-lipoic acid. In this way, mixed micelles containing .alpha.-lipoic acid and purely non-polar but highly lipid soluble antioxidants can be used to convey antioxidants to the tissues.

There are numerous other clinical conditions besides hemorrhagic shock which have as their final common pathway oxidant-inducing injury to tissues which can be treated and/or prevented with the inventive solutions.

#### **CHELATING AGENTS**

According to this invention, the polyaminopolycarboxylic acid, EDTA (ethylene-diaminetetraacetic acid) is provided as a chelating agent for removing toxins such as heavy metals. Additionally, a related polyaminopolycarboxylic acid, diethylenetriaminepentaacetic acid (DTPA) is also provided as a chelating agent that has been shown to have an ability to remove various heavy metals.

According to this invention, EGTA (ethyleneglycol-bis[.beta.-aminoethyl ether]-N,N'-tetraacetic acid) is also provided as chelating agent. EGTA is more specific for particular substances such as calcium when compared to other substances such as magnesium, and thus may be used as a preferred ingredient when it is desirable to chelate calcium (e.g. as is found in arterial plaques, and thus for diminishing arterial plaques) more than for chelating magnesium.

DMSA (dimercaptosuccinic acid) is one effective oral chelating agent that is absorbed orally, and is more effective at chelating particular substances such as mercury, lead, and arsenic in comparison to other substances; and thus DMSA may be used as a preferred ingredient when it is desirable to chelate mercury lead and arsenic (such for the detoxification of poisoning from lead or mercury r arsenic) more than for chelating other substances.

According to this invention, other useful chelating agents are also provided, including diethylenetriamine-pentaacetic acid (DTPA), triethylenetetraaminehexaacetic acid (TTHA), N-hydroxyethylenediaminehexaacetic-acid (HEDHA), 1,4,7-triazacyclononane-N,N',N''-triacetic acid (NOTA), 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA), and N'hydroxyethylenediamine-N,N,N'-triacetic acid (HEDTA).

According to this invention, preferred chelating agents also include iminodiacetic acid (IDA), cyclam, penicillamine, dimercaptosuccinic acid, tartrate, thiomalic acid, crown ethers, nitrilotriacetatic acid (NTA), 3,6-dioxaoctanedithioamide, 3,6-dioxaoctanediamide, salicyladoximine, dithio-oxamide, 8-hydroxyquinoline, cupferron, 2,2'-thiobis(ethyl

acetoacetate), 2,2'-dipyridyl. IDA is a preferred chelating headgroup which is selective for copper ions.

Preferable chelators for use in the present invention include, but are not limited to, ethylenediamine-N,N,N',N'-tetraacetic acid (EDTA); the disodium, trisodium, tetrasodium, dipotassium, tripotassium, dilithium and diammonium salts of EDTA; the barium, calcium, cobalt, copper, dysprosium, europium, iron, indium, lanthanum, magnesium, manganese, nickel, samarium, strontium, and zinc chelates of EDTA; trans-1,2-diaminocyclohexane-N,N,N',N'-tetraacetic acid monohydrate; N,N-bis(2-hydroxyethyl)glycine; 1,3-diamino-2-hydroxypropane-N,N,N',N'-tetraacetic acid; 1,3-diaminopropane-N,N,N',N'-tetraacetic acid; ethylenediamine-N,N'-diacetic acid; ethylenediamine-N,N'-dipropionic acid dihydrochloride; ethylenediamine-N,N'-bis(methylenephosphonic acid) hemihydrate; N-(2-hydroxyethyl)ethylenediamine-N,N',N'-triacetic acid; ethylenediamine-N,N,N',N'-tetrakis(methylenephosphonic acid); O,O'-bis(2-aminoethyl)ethyleneglycol-N,N,N',N'-tetraacetic acid; N,N-bis(2-hydroxybenzyl)ethylenediamine-N,N'-diacetic acid; 1,6-hexamethylenediamine-N,N,N',N'-tetraacetic acid; N-(2-hydroxyethyl)iminodiacetic acid; iminodiacetic acid; 1,2-diaminopropane-N,N,N',N'-tetraacetic acid; nitrilotriacetic acid; nitrilotripropionic acid; the trisodium salt of nitrilotris(methylenephosphoric acid); 7,19,30-trioxa-1,4,10,13,16,22,27,33-octaazabicyclo[11,11,11] pentatriacontane hexahydrobromide; and triethylenetetramine-N,N,N',N'',N''',N'''-hexaacetic acid. It is contemplated that any chelator which binds barium, calcium, cerium, cobalt, copper, iron, magnesium, manganese, nickel, strontium, or zinc will be acceptable for use in the present invention.

More preferably, the chelators for use in conjunction with the present invention may include ethylenediamine-N,N,N',N'-tetraacetic acid (EDTA); the disodium, trisodium, tetrasodium, dipotassium, tripotassium, dilithium and diammonium salts of EDTA; 1,3-diamino-2-hydroxypropane-N,N,N',N'-tetraacetic acid; 1,3-diaminopropane-N,N,N',N'-tetraacetic acid; O,O'-bis(2-aminoethyl)ethyleneglycol-N,N,N',N'-tetraacetic acid; and 7,19,30-trioxo-1,4,10,13,16,22,27,33-octaazabicyclo[11,11,11] pentatriacontane hexahydrobromide.

Most preferably, the chelators for use in the present invention may include ethylenediamine-N,N,N',N'-tetraacetic acid (EDTA); the disodium salt of EDTA; 1,3-diaminopropane-N,N,N',N'-tetraacetic acid; and O,O'-bis(2-aminoethyl)ethyleneglycol-N,N,N',N'-tetraacetic acid.

In a preferred embodiment this invention provides a preparation (or POEBACA), wherein said chelator in said POEBACA may be selected from the group of chelators consisting of EDTA free acid, EDTA 2Na, EDTA 3Na, EDTA 4Na, EDTA 2K, EDTA 2Li, EDTA 2NH<sub>4</sub>, EDTA 3K, Ba(II)-EDTA, Ca(II)-EDTA, Co(II)-EDTA, Cu(II)-EDTA, Dy(III)-EDTA, Eu(III)-EDTA, Fe(III)-EDTA, In(III)-EDTA, La(III)-EDTA, Mg(II)-EDTA, Mn(II)-EDTA, Ni(II)-EDTA, Sm(III)-EDTA, Sr(II)-EDTA, Zn(II)-EDTA, CyDTA, DHEG, DTPA-OH, DTPA, EDDA, EDDP, EDDPO, EDTA-OH, EDTPO, EGTA, HBED, HDTA, HIDA, IDA, Methyl-EDTA, NTA, NTP, NTPO, O-Bistren, and TTHA.

Preferred chelating agents may also be selected from ethylenebis (oxyethylene nitrilio)tetraacetic acid (EGTA) and ethylene diamine tetracetic acid (EDTA), sodium citrate, or oxalate salts such as sodium, potassium, ammonium or lithium oxalate.

Preferred chelating groups include those derived from polyamino-polycarboxylic groups, e.g. those derived from EDTA, DTPA, DOTA, TETA, TITRA or 3,3,9,9-tetramethyl-4,8-diazaundecane-2,10-dione dioxime (HMPAO) or from such groups substituted, e.g. by a p-isothiocyanato-phenyl or 1-3 alkyl, preferably p-isothiocyanatobenzyl. Chelating groups derived from DTPA are also preferred.

In a preferred embodiment this invention provides a preparation (or POEBACA), wherein the chelating group is derived from ethylene diaminetetraacetic acid (EDTA), diethylene triamine pentaacetic acid (DTPA), ethylene glycol-0,0'-bis(2-aminoethyl)-N,N',N'-tetraacetic acid (EGTA), N,N'-bis(hydroxybenzyl)ethylenediamine-N,N'-diacetic acid (HBED), triethylenetetramine hexaacetic acid (TTHA), substituted EDTA or -DTPA 1,4,7,10-tetra-azacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA) and 1,4,8,11-tetraazacyclotetradecane-N,N',N'',N'''-tetraacetic acid (TETA), in free form or in pharmaceutically accepted salt form.

In a preferred embodiment this invention provides a preparation (or POEBACA), wherein the chelating group is derived from 1,4,7,10-tetraazacyclotridecane-1,4,7,10-tetraacetic acid (TITRA), 1,4,8,11-tetraazacyclotetradecane (TETRA); EDTA, DTPA, DOTA, TETA, TITRA, TETRA or 3,3,9,9-tetramethyl-4,8-diazaundecane-2,10-dione dioxime (HMPAO)

substituted by p-isothiocyanato-phenyl-C.sub.1-3 alkyl, in free form or in pharmaceutically accepted salt form.

In a preferred embodiment this invention provides a preparation (or POEBACA), comprising R/S-.gamma.-lipoic acid (6,8-dimercaptooctanoic acid) or R/S-.alpha.-lipoic acid (D,L-thioctic acid).

According to separate but non-limiting embodiments of this invention, "substantially enantiomerically pure" 1,2-dithiolane-3-pentanoic acid (thioctic acid, .alpha.-lipoic acid) is within the range from at least about 80% pure to at least about 99% pure inclusive as well as every 1% increment within this range (i.e. at least about 80% pure, at least about 81% pure, at least about 82% pure, etc.).

According to another embodiment of this invention, D,L-thioctic acid can be used in the form of the racemic mixture. According to this invention, a racemic mixture can be comprised of two isomers that are found at a ratio within the range from about 20%:80 % to about 80%:20% inclusive as well as every 1% increment within this range (i.e. about 20%:80%, about 21%:79%, about 22%:78%, etc.).



According to another embodiment of this invention, optically active R-(+)-.alpha.-lipoic acid is used. R-(+)-.alpha.-lipoic acid is a natural substance that is found in animals and humans, and it acts as coenzyme in the oxidative decarboxylation of .alpha.-keto acids.

### **Microspheres**

Specific, but non-limiting, examples of microspheres according to this invention are provided herein. Specific, but non-limiting, examples of ways of making, administering, and using microspheres according to this invention are provided herein. In separate non-limiting embodiments, this invention provides that the microspheres can be made using lecithin (and/or alternative ingredients as per Table 1 and 2) in amounts in the range from about 0.1 gram to about 40 grams inclusive, including specifically each increment of about 0.1 gram within this range, in a total of 2 ounces of final POEBACA product.

In one embodiment, this invention provides POEBACA comprising gas-filled microspheres. The invention further relates to methods for employing such microspheres as delivery systems to deliver the POEBACA.

In one embodiment, this invention provides POEBACA comprising at least one member selected from the group consisting of animal and vegetable oils, hydrocarbon oils, ester oils, silicone oils, higher fatty acids, higher alcohols, sunscreens, vitamins, alpha lipoic acid, ferulic acid, and flavors and said solid or semi-solid oil component is at least one member selected from the group consisting of animal and vegetable oils, hydrocarbon oils, ester oils, higher fatty acids, higher alcohols, waxes, sunscreens and flavors

### Example 2

	INGREDIENTS:	per 2 fl oz	%
	Lecithin	30.0 gm	50
	EDTA (e.g. Disodium EDTA)	1.0 gm	1.7
	Magnesium Chloride	150.0 mg	0.26
	Alpha Lipoic Acid	100.0 mg	0.17
	Purified Water		37.3
	Ethyl Alcohol		10
	Gum Arabic		0.5

- 1) Dissolve alpha lipoic acid and EDTA in half the amount of alcohol.
- 2) Disperse lecithin in half the amount of alcohol and equal amount of water  
Heat to 50C, mix with high shear mixing or sonication (sufficient to form micropsheres or liposomes) for 20 minutes, cool to 40C.
- 3) Add magnesium chloride and gum arabic to the remaining amount of water,  
Stir for 30 minutes at room temperature
- 4) Add step number 3 to step number 2. Mix for 20 minutes
- 5) Add step 4 to step 1, stir gently for 20 minutes.
- 6) Take a random samples and test for the presence of liposomes.

### Example 3

	INGREDIENTS:	per 2 fl oz	%
	Lecithin	30.0 gm	50
	EDTA (e.g. Disodium EDTA)	1.0 gm	1.7
	Magnesium Chloride	150.0 mg	0.26
	Alpha Lipoic Acid	100.0 mg	0.17
	Purified Water		37.3
	Ethyl Alcohol		10
	Gum Arabic		0.5

- 1) Dissolve alpha lipoic acid in half the amount of alcohol.
- 2) Disperse lecithin in half the amount of alcohol and equal amount of water  
Heat to 50C, mix with high shear mixing or sonication (sufficient to form micropsheres or liposomes) for 20 minutes, cool to 40C.
- 3) Add EDTA, magnesium chloride and gum arabic to the remaining amount of water,  
Stir for 30 minutes at room temperature
- 4) Add step number 3 to step number 2. Mix for 20 minutes
- 5) Add step 4 to step 1, stir gently for 20 minutes.
- 6) Take a random samples and test for the presence of liposomes.

### Example 5

	INGREDIENTS:	per about 760 mg	%
	Di-indolemethane	100 mg	13.15
	Grape (skin) extract	200 mg	26.3
	Calcium D-Glucarate	200 mg	26.3
	Medium chain triglycerides (MCTs)	50 mg	6.58
	Lecithin (Phosphatidyl choline 20-30%)	50 mg	6.58

#### OTHER INGREDIENTS:

Cellulose powder(13.52%), magnesium silicate (5.65%), magnesium stearate (0.52%), silicon dioxide(1.34%)

**CAPSULE SIZE:** "00" Vcaps  
**CAPSULE FILL:** 760 mg

#### PREPARATION:

1. Sift calcium-D-glucarate into a planetary mixer (e.g. Hobart) or v-blender tumbler through # 18 mesh screen.
2. Sift Grape skin extract into a planetary mixer (e.g. Hobart) or v-blender tumbler through # 18 mesh screen. Mix for 8+ minutes
3. Sift DIM into a planetary mixer (e.g. Hobart) or v-blender tumbler through # 18 mesh screen. Mix for 8+ minutes
4. Sift MCTs, magnesium silicate and lecithin into a planetary mixer (e.g. Hobart) or v-blender tumbler through # 18 mesh screen. Mix for 8+ minutes
5. Sift Cellulose powder into a planetary mixer (e.g. Hobart) or v-blender tumbler through # 18 mesh screen. Mix for 8+ minutes
6. Sift magnesium stearate and silicone dioxide through # 40 mesh screen into the mixer, mix for 4+ minutes.

For example, indole-3-carbinol (I3C) and its dimer 3,3'-diindolylmethane (DIM), obtained from dietary consumption of cruciferous vegetables, have multiple biochemical activities. Both compounds have been reported to be clinically effective in treating precancerous lesions of the cervix and laryngeal papillomas, pathologies with a human papillomavirus (HPV).

Various modifications of the invention in addition to those shown and described herein will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims.

In a preferred embodiment this invention provides a preparation (or POEBACA), comprising ocular drug delivery vehicle of an oil-in-water submicron emulsion consisting essentially of about 0.5 to 50% of a first component of an oil, about 0.1 to 10% of a second component of an emulsifier, comprising a phospholipid, about 0.05 to 5% of a non-ionic surfactant and an aqueous component, said submicron emulsion having a mean droplet size in the range of 0.05 to 0.5  $\mu\text{m}$ , and a weight ratio of surfactant to oil of about 1:1 or less.

In a preferred embodiment this invention provides a method for transferring ingredients making up a preparation of encapsulated bioavailable chelating agents (i.e. POEBACAI) across a cellular membrane by encapsulating said ingredients within liposomes and carrying said POEBACAI to the cellular membrane where the liposomes will be taken up by the cells, thereby transferring the POEBACAI across the cellular membrane. POEBACAI can be introduced into the interior of a cell of a living organism wherein the liposomes will be decomposed, releasing the POEBACAI to the interior of the cell. The released POEBACAI will complex intracellularly deposited toxic heavy metals, permitting the more soluble metal complex to transfer across the cellular membrane from the cell and subsequently be removed from the living organism.

In a preferred embodiment this invention provides a method of transferring POEBACAI across a cellular membrane comprising: encapsulating said POEBACAI within liposomes; and carrying said liposome encapsulated POEBACAI to said cellular membrane, whereby said liposome encapsulated POEBACAI will transfer across said cellular membrane.

**In a preferred embodiment this invention provides a method of introducing a POEBACAI into the interior of a cell in accordance with the method of claim 1 wherein said cellular membrane is the membrane wall of said cell and said encapsulated POEBACAI passes through the membrane wall of said cell into the interior of said cell, wherein said liposomes will be decomposed, thereby releasing said POEBACAI to the interior of said cell.**

**In a preferred aspect this invention provides a method wherein said cell is a cell of a living organism and said POEBACAI is carried to said cell by injecting a saline suspension of said liposome POEBACAI into the blood stream of said living organism whereby said POEBACAI is carried to the cell within the blood**

**In a preferred embodiment this invention provides a method for the removal of intracellularly deposited toxic heavy metals comprising:**

**encapsulating a POEBACAI agent within liposomes;**

**introducing said liposomal POEBACAI into the blood system by one or more of the following routes: oral administration, intravenous injection, transdermal patch; whereby**

**said liposome POEBACAI is carried to said body cells within said blood system;**

**said liposome POEBACAI is passed through the cell wall into the interior of said body cell;**



said POEBACAI is released to the interior of said cell by the biological degradation of said liposome by lysosomal enzymes, said released POEBACAI complexing said intracellularly deposited toxic metal;

said complexed toxic metal is passed through the cell wall into said blood stream; and

said complexed toxic metal is removed from said blood stream and the body by normal body processes.

In a preferred embodiment this invention provides a preparation of POEBACA wherein said liposomes are prepared from a mixture of lecithin and cholesterol.

In a preferred embodiment this invention provides a POEBACAI comprised of a member chosen from the group consisting of EDTA, EGTA, and DTPA.

In a preferred embodiment this invention provides a detoxification method wherein said toxic heavy metals are selected from the group consisting of plutonium, gold, mercury, and lead, beryllium, and cadmium.

Any gel can be used in the practice of the present invention. The materials which can be used to form such gels include but are not limited to: carbohydrates such as cellulose,

methylcellulose, starch and modified starch, agarose, gum arabic, ghatti, karay, tragacanth, guar, locust bean gum, tamarind, carageenan, alginate, xanthan, chickle, collagen, polyacrylamide, polysiloxanes (polyanhydrides, e.g., malic anhydride copolymers, polyacrylates, e.g., hydroxyethylpolymethacrylate polymethylmethacrylate, polyethylethacrylate polymethacrylate, ethylenevinylacetate copolymers, ethylenevinylalcohol copolymers, polyorthoesters, .epsilon.-caprolactones, amino acid polymers such as gelled albumin, amino acid polymers and copolymers and gelatins, and other organic or inorganic polymers which can be mixed with liposomes in vitro.

After the mixture forms a gel the resulting liposome-gel matrix can be implanted in tissues.

In a particularly useful embodiment of the present invention soft gel matrices such as agarose, collagen and the like containing sequestered liposomes may be injected in vivo. Alternatively, gels such as methylcellulose can be formed in the tissues after inoculation of liposomes in a suspension containing the gel material. After inoculation the suspension forms a gel and the liposomes remain sequestered in the gel matrix rather than dispersed and cleared. Regardless of the method used for preparing and implanting the gel matrix, the release of a liposome entrapped bioactive chelating agent or other POEBACAI is prolonged and the relative concentration of the agent at the site of inoculation is increased.

Virtually any POEBACAI (including chelating agents) as well as virtually any other bioactive agent can be entrapped within the liposomes for use according to the present invention. Such agents include but are not limited to antibacterial compounds, antiviral compounds, antifungal compounds, anti-parasitic compounds, tumoricidal compounds,

proteins, toxins, vitamins, trace minerals, heavy metals, enzymes, hormones, neurotransmitters, lipoproteins, glycoproteins, immunoglobulins, immunomodulators, dyes, radiolabels, radio-opaque compounds, fluorescent compounds, polysaccharides, cell receptor binding molecules, anti-inflammatories, antiglaucomic agents, mydriatic compounds, anesthetics, nucleic acids, polynucleotides, etc.

In fact, if concurrent therapy is desired, two or more POEBACAI (including chelating agents) or other bioactive agents may be entrapped in one liposome population which is sequestered in the gel matrix. Alternatively, two or more liposome populations (of the same or different types of liposomes, e.g. mixtures of SPLVs, MPVs, SUVs, LUVs, REVs, etc.) which each entrap the same or different POEBACAI (including chelating agents) or other bioactive chelating agents may be sequestered in the gel matrix.

In yet another embodiment of the present invention the gel can be used as a vehicle for the same or different bioactive chelating agents and other POEBACAI than those entrapped by liposomes.

In certain therapeutic applications it may be desired to deliver a relatively high dose of a drug compound (i.e., compound A) followed by a sustained dose of the same or another compound (i.e., compound B). According to the present invention, this is readily accomplished by entrapping compound B in liposomes, sequestering the liposomes in a gel matrix containing compound A, and administering the same in vivo in a single inoculation.

Thus, rapid delivery of compound A by diffusion from the gel, and slow sustained delivery of compound B by release from the liposomes is effected

The release of the bioactive chelating agents may be controlled by the type of liposomes used and the membrane composition of the liposome bilayers as well as by the type and porosity of the gels used. The rate of release is also dependent upon the size and composition of the bioactive chelating agent itself. The liposome itself is the first rate limiting factor in the release of entrapped bioactive chelating agents. The rate of release may depend upon the number of bilayers, the size of the liposomes and most importantly the bilayer composition.

A number of researchers add "stabilizers" such as sterols, cholesterol and the like to the phospholipid bilayers in order to alter the permeability of the liposome (Papahadjopoulos, D., Kimilberg, H. K., 1974, in *Progress in Surface Science*, ed. S. G. Davison, pp. 141-232, Oxford: Pergamon; Demel, R. A., Bruckdorf, K. R., Van Deenan, L. L., 1972, *Biochem. Biophys. Acta*, 255:331-347). For the present invention it is important that the stable liposomes will release their contents upon contact with body fluids or culture media. The rate of release may be controlled by modifying liposome membranes accordingly using known methods.

### **Use of the Liposome-Gel Preparation in Living Systems.**

The liposome-gel compositions of the present invention may be used for sustained delivery of a bioactive chelating agent to cells and/or fluids in vivo and in vitro.

When used in vivo, the liposome-gel compositions of the present invention may be administered before or after gel formation. Routes of administration include but are not limited to: inoculation or injection, (e.g., intraperitoneal, intramuscular, subcutaneous, intra-aural, intra-articular, intra-mammary, etc.), topical application (e.g., on areas, such as eyes, ears, skin or on afflictions such as wounds, burns, etc.), and by absorption through epithelial or mucocutaneous linings (e.g. vaginal and other epithelial linings, gastrointestinal mucosa, etc.).

For example the liposome-gel preparations of the present invention may be inoculated in vivo to provide for the sustained systemic release of the bioactive chelating agent. Such applications may be particularly useful for the systemic release of drugs such as hormones (e.g., to control growth, fertility, sugar metabolism, etc.) or antimicrobials to control and treat infections, etc.

In an alternative example, the liposome-gel preparation may be applied topically. Topical application may be particularly useful for the treatment of wounds (either surgical or non-surgical wounds) where the sustained release of POEBACAI (including chelating agents), antimicrobials and/or blood clotting factors may be helpful in the healing process. Similarly, the liposome-gel preparation may be topically applied to burns for the sustained release of

POEBACAI (including chelating agents), antimicrobials and/or cell growth factors. The liposome-gel preparation may also be applied in the ear to treat infections by providing sustained release of POEBACAI (including chelating agents), antimicrobials; this would reduce the necessity of repeated applications of the bioactive chelating agent in the form of ear drops.

In another alternative embodiment, a liposome-gel preparation may be administered orally for sustained release. Such application may be useful for sustained release to oral epithelium and other oral tissues and for sustained release to epithelia of the alimentary tract.

The liposome-gel preparations of the present invention may also be used in vitro to provide for sustained release of a POEBACAI (including chelating agents) into the cell or tissue culture medium. Such POEBACAI (including chelating agents) may also include but are not limited to nutrients, drugs, hormones, growth factors, etc. The liposome-gel preparation may be used as a support for cell adhesion and growth; for instance, a liposome-collagen gel may be especially useful for culturing muscle cells, nerve cell, or liver cells. When the liposome-gel preparation is applied as an overlay, a liposome-agarose gel may be particularly useful.

## REFERENCES

Many methods for making preparations comprising the ingredients provided herein as well as methods for making preparations comprising microspheres or liposomes are many in the art. For particularly useful references regarding these methods, see the references listed below, which are hereby incorporated by reference in their entirety.

The following US patents are hereby incorporated by reference herein in their entirety:

5,990,153; 5,000,887; 4,994,213; 4,981,692; 4,975,282; 4,963,297; 4,952,405; 4,944,948; 4,927,637; 4,927,571; 4,923,854; 4,906,476; 4,897,384; 4,895,719; 4,891,208; 4,885,172; 4,880,635; 4,873,088; 4,861,580; 4,839,175; 4,837,028; 4,828,837; 4,822,777; 4,818,537; 4,804,539; 4,781,871; 4,766,046; 4,762,915; 4,752,425; 4,737,323; 4,721,612; 4,714,571; 4,708,861; 4,698,299; 4,668,638; 4,666,831; 4,610,868; 4,588,578; 4,564,599; 4,522,803; 4,483,929; 3,932,657; 3,909,284; and 3,576,663.

The following references are also hereby incorporated herein in their entirety:

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## **CLAIMS**

- 1. An orally ingestible preparation comprised of the following ingredients:**
  - a) one or more members selected from the group consisting essentially of plant indoles, e.g. as diindolemethane, and sources of plant indoles;**
  - b) one or more members selected from the group consisting essentially of plant flavonoids, polyphenols, stilbenes and related substances, e.g. resveratrol and piceatannol, and sources of plant flavonoids, polyphenols, stilbenes, and related substances**
  - c) one or more members selected from the group consisting essentially of D-glucaric acid and derivatives thereof, e.g. calcium D-glucarate and 1,4-GL, and sources thereof;**
  - d) one or more members selected from the group consisting essentially of medium chain triglycerides or MCTs and sources thereof; and**
  - e) one or more members selected from the group consisting essentially of phospholipids, e.g. phosphatidyl choline, and sources thereof, e.g. lecithin.**

## **ABSTRACT**

Novel preparations of phytochemical ingredients that are serviceable as health supplements for the body, particularly tissues susceptible to cancer, including, e.g. prostate tissue and breast tissue and, including, e.g., female breast tissue; for example, all possible combinations and permutations of member from each of the following 5 groups: 1) plant indoles, including sources of plant indoles (e.g. diindolemethane); 2) plant flavonoids, polyphenols, stilbenes and related substances, including sources of plant flavonoids, polyphenols, stilbenes, and related substances (e.g. resveratrol and piceatannol); 3) D-glucaric acid and derivatives thereof (e.g. calcium D-glucarate and 1,4-GL) and sources thereof; 4) medium chain triglycerides and sources thereof; and 5) phospholipids and sources thereof (e.g. lecithin).